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Co- infection of Multidrug-resistant tuberculosis and HIV: Implication for Public Health. Review

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Abstract

This article describes the current status of MDR-TB and the epidemic of MDR-TB and HIV co-infection in worldwide. TB is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* that transmitted through aerosol droplets and one of the world's most devastating human pathogens that cause more than 2 million deaths annually. On the other hand, Multidrug-resistant tuberculosis (MDR-TB) caused by *M. tuberculosis* strains resistant to at least isoniazid (INH) and rifampin (RMP) has emerged as a significant global epidemic resulting largely from deficiencies in TB case management and program management. Subsequently, there are alarming reports of increasing drug resistance from various parts of the globe. Moreover, the most important risk factor for the development of MDR-TB is previous anti-tuberculosis therapy. Studies indicated that approximately 425,000 MDR-TB cases occur annually worldwide, representing nearly 5% of the world's annual TB burden. On the other hand, the human immunodeficiency virus (HIV) is a driving force behind the global burden of TB and the development of drug-resistant TB. Obviously, the growing HIV infection epidemic presents massive challenges to TB control programs at all levels and could fuel further increases in anti-TB drug resistance and hence people living with HIV have a higher risk of MDR. The synergy between TB and HIV is strong; in high HIV prevalence population, TB is a leading cause of morbidity and mortality. Therefore, managing the treatment of existing cases properly is the key in prevention of the spread of MDR-TB through taking all of the medications exactly as prescribed by the healthcare providers.

Keywords: HIV, MDR-TB, *Mycobacterium tuberculosis*, Prevalence, Risk factor

1. Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* that most commonly affects the lungs and remains one of the world's deadliest communicable diseases (Raviglione*et al.*, 2012; Zhao *et al.*, 2012; WHO, 2014a). It continues to be a major public health problem in the worldwide and one-third of the world population was infected by *Mycobacterium* (Sohail, 2006; Dara *et al.*, 2009). Moreover, it ranks as the second leading cause of death worldwide from a single infectious agent, after the human immunodeficiency virus (WHO, 2013). It is spread by people with active respiratory disease through the air. People who have TB disease in their lungs can release tiny particles containing *Mycobacterium tuberculosis* into the air by coughing, sneezing or even talking (WHO, 2012 and TB Alliance, 2012b). TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys or the spine.

Still, TB is a leading cause of death by an infectious disease worldwide, despite global efforts and financial investment by governments and non-govern mental organizations in disease control programmes during the past 20 years (Raviglione*et al.*, 2012). In most cases, although TB is treatable and curable, persons with TB can die if

they do not get proper treatment (CDC, 2012).According to the report of WHO,in 2013, about 9.0 million people developed TB and 1.5 million died from the disease, of these 360 000 were HIV-positive (WHO, 2014a).

As global status of Tuberculosis indicated, TB remains a major global public health concern (Zhao*et al.*, 2012). Worldwide, about 8.6 million new TB cases in 2012 were reported and 1.3 million die every year as a result of TB (WHO, 2013). Global control of TB has been making vulnerable by two major threats: Multi-drug resistant tuberculosis (MDR-TB) and HIV/AIDS.

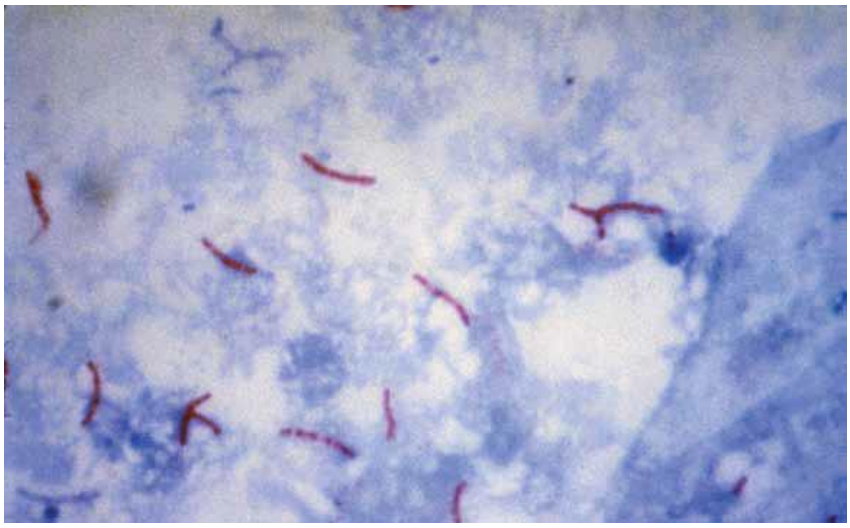

Figure 1.*Mycobacterium tuberculosis* bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X.

TB is considered drug-resistant (DR) when the organism (mycobacterium tuberculosis) is not killed by anti-TB drugs. And this can be confirmed by a laboratory test called drug susceptibility test (DST). **Primary resistance -** is resistance in cultures from patients with no history of previous TB treatment or patients who had received TB treatment for less than one month. Resistance in new patients provides a measure of the degree of transmissionof*M. tuberculosis* strains.

Acquired/secondary resistance - refers to resistance in cultures from patients with one or more previous TB treatment episodes, of more than one month each. Resistance levels in retreatment are always higher than in new patients, and provide an indication of the extent to which patients were appropriately treated, i.e. the quality of TB control.

Drug-resistant TB is disease (usually pulmonary) caused by *M. tuberculosis* resistant to one or more anti-TB drugs. The terms ‘primary’ and ‘acquired’ have been discontinued as epidemiological terminology, as the exact causative nature of drug resistance in a patient is not always possible to assess. Patients may be erroneously labeled as having primary resistance if they do not disclose previous treatment for TB, while patients who fail treatment (and are therefore labeled to have acquired resistance) may do so because the initial strain was resistant and not because it acquired resistance during treatment. The overall prevalence of drug resistance is often related to the number of previously treated cases in the country. In previously treated patients, the probability of any resistance was over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients.

For example, chronic cases of TB (defined by the WHO as cases of tuberculosis that have failed a supervised retreatment regimen) often have MDR-TB. However, there is no way to know if a chronic case of TB has acquired TB or primary TB unless drug susceptibility testing (DST) to the strain was performed at the start of the patient's treatment and then documented to acquire resistance.

Drug resistance in tuberculosis is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by anti-TB drugs. The problem is greatly exacerbated by inadequate treatment such as direct or indirect monotherapy, resulting from intake of a single anti-TB drug or from intake of several drugs with suboptimal concentrations. Susceptible bacilli are killed rapidly and resistant mutants are then able to multiply.

Mycobacterium tuberculosis has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms(Gillespie, 2002; Huitric*et al.,* 2010). This natural phenomenon is genetically determined and varies from drug to drug. The probability of spontaneous resistance to individual first-line anti-TB drugs is as follows(Bergval*et al.,* 2009; Bergval*et al.,* 2012; Stoffels*et al.,* 2012):

- **Isoniazid:** one in every 10^6 cell divisions.
- **Rifampicin:** one in every 10^9 cell divisions.
- **Streptomycin:** one in every 10^6 cell divisions.
- **Ethambutol:** one in every 10^5 cell divisions.
- **Pyrazinamide:** one in every 10^5 cell divisions.

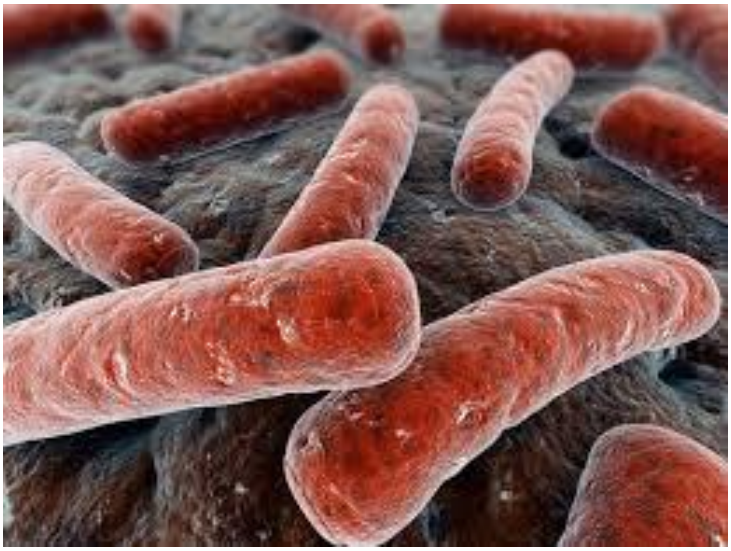

Figure 2. *Mycobacterium tuberculosis*

Typically, the chromosomal location of resistance to different drugs is not linked; therefore, spontaneously occurring multidrug resistance is extremely rare. For example, the probability of mutation resulting in resistance to isoniazid is 10^{-6} and for rifampicin it is 10^{-9}. The likelihood of spontaneous resistance to both isoniazid and rifampicin is the product of the two probabilities, i.e. 10^{-15}. Since the probability of naturally occurring resistant mutants is very low, a large bacterial load (eg. in lung cavities) is needed for MDR-TB strains to emerge.

MDR-TB is not the same as disease due to non-tuberculous mycobacteria (NTM). The latter arecommonly resistant to both isoniazid and rifampicin but should not be confused with MDR-TB. This training course is relevant for the management of MDR-TB only and not for disease caused by NTM. Identification of NTM disease is made after the culture has been referred for specialized identification. NTM are often contaminants in

the sputum and are only of clinical significance when several bacteriological, radiological and clinical criteria have been met(Madkour, 2004; Shahram*et al.,* 2013).

The term **MDR-TB** has a very specific definition in the field of medicine. A strain of *Mycobacterium tuberculosis* that is resistant to the effects of at least isoniazid and rifampicin is defined as a MDR-TB, withor without resistance to any other drugs. Isoniazid and rifampicin are the two most potent drugs availablefor TB treatment.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to being MDR-TB. Four different categories of drug resistance have been established:

- Mono-resistance: resistance to one antituberculosis drug;
- Poly-resistance: resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin;
- Multidrug-resistance: resistance to at least one isoniazid and rifampicin;
- Extensive drug-resistance: resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug-resistance.

According to WHO documents, MDR-TB is a particularly complicated form of TB characterized by resistance to at least isoniazid (INH) and rifampicin (RMP), the two most potent TB drugs. These drugs are used to treat all persons with TB disease (WHO 2008; WHO, 2012). On the other hand, since these two drugs are the two most important first-line TB drugs, their removal through resistance from the anti-TB drug armamentarium has serious implications. Moreover in earlier report indicated that at any given time, about 630 000 people in the world are thought to carry strains of *M. tuberculosis* showing resistance to these two drugs that are currently the most effective against TB (Dye, 2006).

In addition, extensively drug resistant TB (XDR-TB) is a rare type of MDR-TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin (Biadglegne*et al.,* 2014). Since XDR-TB is resistant to first-line and second-line drugs, patients are left with treatment options that are more toxic, more expensive, and much less effective (TB Alliance, 2012a).

According to a recent WHO document, while MDR- TB is often curable, treatment is complex, requiring expert management and frequent monitoring. In comparison with drug-susceptible TB, which takes about 6 to 9 months to treat, recommended treatment for MDR- TB lasts 18 to 24 months or longer (WHO, 2013). Furthermore MDR-TB also requires the use of second-line medicines that are not as effective as the first-line medicines commonly prescribed to treat TB (CDC, 2014; Nishi *et al.*, 2014). The second-line medicines may also produce side effects that are difficult to tolerate. To this view, as study indicated drug resistant strains of *Mycobacterium tuberculosis* is of great concern, because it requires the use of second-line drugs that are difficult to procure and are much more toxic and expensive than the first-line regimen (Espinal*et al.*, 2001). Thus, close monitoring of patients while taking these drugs is critical, because the medications can also lead to other serious health problems, such as damage to the kidneys, liver, or heart; loss of vision or hearing; and changes in behavior or mood including depression or psychosis (Marks *et al.,* 2014).

1.1. Spread and manifestations of MDR-TB and Causes of MDR-TB

Both the drug susceptible and resistant MTB spread in the same manner, and also the symptoms do not differ. Cough of two or more weeks is the main symptom with or without fever, chest and/or back pains, hemoptysis, significant weight loss, and others like sweating, fatigue, body malaise and shortness of breath.

Although its causes are microbial, clinical and programmatic, DR-TB is essentially a man-made phenomenon (WHO, 2009). From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1summarizes the common causes of inadequate treatment although MDR-TB can then spread from one person to another (Jennifer, 2010).These potential causes of inadequate treatment can be broadly categorized in to:-

- Health care factors: provider, program related factors
- Drug related factors and Patient related factors.

Table 1. Causes of inadequate Anti- tuberculosis treatment(Source: adapted from FMOH, 2008).

Health-care provider/program related factors:	**Drug related factors: inadequate supply or quality**	**Patient- related factors: inadequate drug intake**
• Inappropriate • guidelines • Non-compliance with guidelines • Absence of guidelines • Poor training • Poor supervision • No monitoring of treatment provision • Poorly organized or funded TB control program • Inadequate regimens • Lack of DST • Poor access to health care	• Poor quality • Unavailability of certain drugs due to stock-outs of delivery disruptions • Poor storage conditions • Wrong doses or combinations (manufacture related)	• Poor adherence/default • Lack of or inadequate patient information • If Treatment not given for free • Lack of transportation money or support • Drug adverse effects/interaction, • Social barriers • Mal-absorption • Substance/alcohol dependence

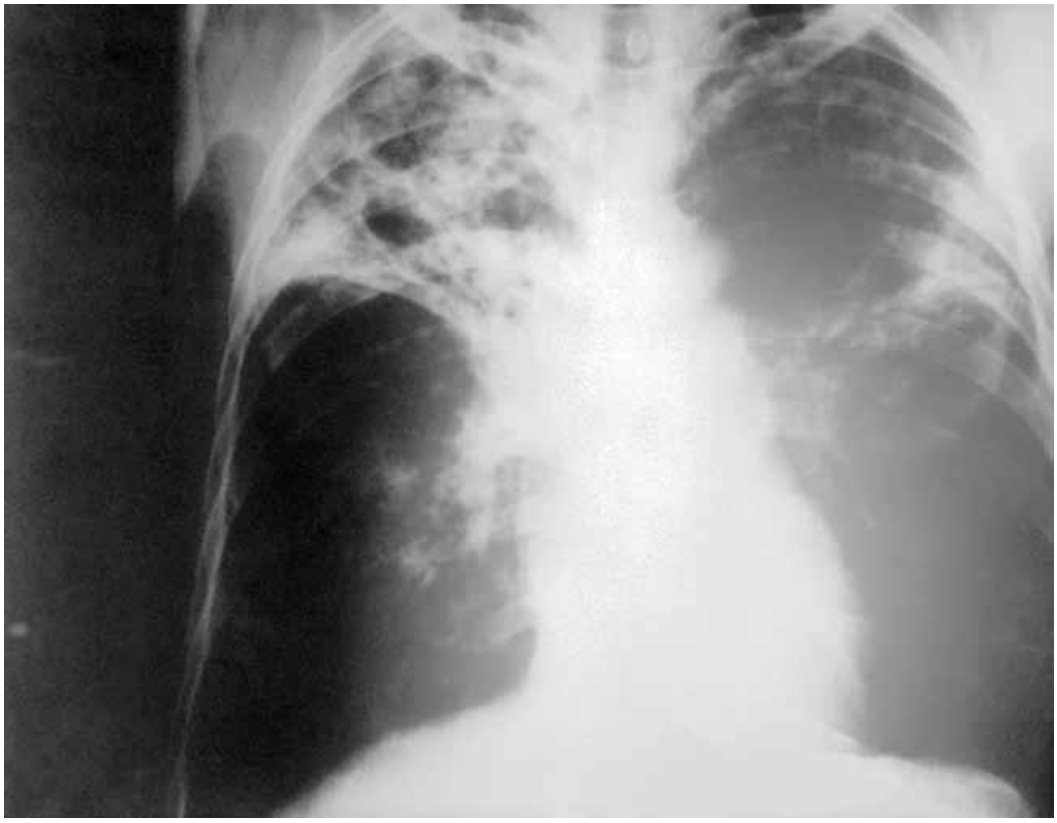

Figure 3. An anteroposterior X-ray of a patient diagnosed with advanced bilateral pulmonary TB. MDRTB cannot be diagnosed by X-ray alone.

1.2 MDR-TB treatment outcomes

Outcomes definitions rely on the use of laboratory smear and culture as a monitoring tool (Anderson *et al.*, 2013; Migliori, 2012):

a) **Cured:** MDR-TB patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

b) **Treatment completed:** MDR-TB patient who has completed treatment according to programme protocol but does not meet the definition cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).

c) **Died:** MDR-TB patient who dies for any reason during the course MDR-TB treatment.

d) **Failed:** Treatment will be considered to have failed if two or more of five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do sub-analysis).

e) **Defaulted:** MDR-TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.

f) **Transferred out:** MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

• Patients who have been transferred in should have their outcome reported back to treatment centre from which they originally were registered. The responsibility of reporting their final outcomes belongs to the original treatment center.

Treatment of Drug resistant Tuberculosis

Groups of Anti-TB Medications

Drugs with anti-TB effect are classified into five groups as summarized in the table below.

Table 2. Grouping of anti-tuberculosis agents (Source: adapted from (Tahaoglu*et al.,* 2001; Bai *et al.,* 2007; WHO, 2008).

Grouping	**Drugs**
Group 1: First-line oral agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable agents	Streptomycine (S), Kanamycin (Km); Amikacin (Am); Capreomycin (Cm);
Group 3: Fluoroquinolones	Ofloxacillin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx)
Group 4: Oralbacteriostatic second-line agents	Ethionamide (Eto); Prothionamide (Pto), Cycloserine (Cs); *para*-aminosalicylic acid (PAS)
Group 5: Agents with unclear role in DR-TB treatment (not recommended by the WHO for routine use in DR-TB patients)	Amoxicillin/clavulanate (Amx/Clv); Clarithromycin (Clr); High-dose isoniazid (High-dose H);[a] Clofazimine (Cfz);Linezolid (Lzd); Thioacetazone (Thz); Imipenem/cilastatin (Ipm/Cln);

- [a]High-dose H is defined as 16-20 mg/kg/day.
- **Mono-resistance:** resistance to one anti-tuberculosis drug.
- **Poly-resistance:** resistance to more than one ant-ituberculosis drug, other than

Designing MDR-TB treatment regimen

As with drug-susceptible TB, the use of multiple drugs is imperative to prevent the development of additional resistance. Consideration of cross-resistance is also important when designing treatment regimens for MDR-TB (Burgos *et al.*, 2005; Migliori, 2012).

Principles of Designing MDRTB Treatment regimen

- Start with first line drugs if sensitivity confirmed
- Treatment regimens should consist of at least four drugs with either certain, or almost certain effectiveness
- Always add one from the injectable groups (Am/Km, Cm) and one from flouroquinolones (Lfx, Mfx); add new drugs from the other group until there are 4 effective drugs in the regimen.
- As standard all patients will receive Pyrazinamide, Kanamycin/Amikacin, Levofloxacin, Ethionamide, and Cycloserine
- Ethambutol is continued if DST suggests susceptibility to the drug. However, as most patients have already used Ethambutol for prolonged periods and DST for Ethambutol is not fully reliable, this drug will not count as one of the 4 effective drugs 'with certain effectiveness', even if the DST shows susceptibility
- Pyrazinamide will be used throughout the course of treatment as resistance uncommon and no reliable DST available, but it is not counted as an effective drug. MDR TB patients have extensive lung damage with cavities and fibrosis creating an acidic media. Pyrazinamide can act against mycobacteria in this acidic media.
- The drugs dosages are determined by body weight (ISTC, 2009).

Duration and Phases of Treatment

Intensive phase*:* refers to the initial period of treatment when maximal bacillary load reduction is aimed. This period is noted by the presence of injectable drug.

The recommended duration of administration of the injectable agent (or the intensive phase), is guided by smear and culture conversion.The current recommendation is that the injectable agent should be continued for minimum of 8 months and at least 4 months after culture conversion(Gyanshankar*et al.*, 2014).

It is further recommended that culture results, chest x-ray findings and the patient's clinical status be taken into account in deciding whether or not to continue an injectable agent for longer, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present (Migliori, 2012).

Continuation phase*:* refers to the period where the injectable drug is discontinued and patient continues to take oral drugs. The duration of treatment is guided by culture conversion. And treatment should be continued for a minimum of 18 months beyond culture conversion (Gyanshankar*et al.*, 2014).

MDRTB regimens in different conditions

A. Management of Extra-pulmonary MDR-TB

Extra-pulmonary MDR-TB is treated with the same strategy and duration of treatment as pulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs which have adequate penetration into the central nervous system. Pyrazinamide, ethionamide and cycloserine have good penetration into the cerebrospinal fluid (CSF); kanamycin, amikacin, and capreomycin do so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable CSF penetration, with better penetration seen with the higher generations (Migliori, 2012).

B. Management of Mono and Poly-drug Resistant TB

Mono-resistance refers to resistance to a single first-line drug while poly-resistance refers to resistance to two or more first-line drugs but no resistance to the combination of rifampicin and isoniazid (WHO, 2014c). Cases with mono or poly-resistance will be identified during the course of case-finding for M(X)DR-TB (Migliori, 2012).Treatment of patients infected with mono or poly-resistant strains using standardized short-course chemotherapy has been associated with increased risk of treatment failure and further acquired resistance, including the development of M(X)DR-TB.

MDR- TB in special conditions and situation

Special conditions that need to be considered in the management of patients with MDR TB (WHO, 2014c):

- Pregnancy
- Breast feeding
- Contraceptive use
- Co-morbidities such as Diabetes Mellitus, Renal Insufficiency, Liver disease, Seizure disorders , Psychiatric disorders and Substance abuse

Pregnancy and MDR-TB

Treatment of drug-resistant tuberculosis (TB) during pregnancy is very challenging. All female patients of childbearing age with multidrug-resistant TB (MDR-TB) should be strongly advised to avoid pregnancy. Some clinicians do monthly laboratory screening to detect pregnancy early (Drobac*et al.,* 2005; Khan *et al.,* 2007; Tabarsi*et al.,* 2007; WHO, 2014c).

Pregnancy is not a contraindication for treatment of drug-resistant TB (Bergeron *et al.,* 2004). Consider risks and benefits to fetus and mother. The effect of second line anti TB drugs on the human fetus is not yet fully understood. All female patients of childbearing age should be tested for pregnancy upon initial assessment. Last Menstrual Period (LMP) should be asked routinely during each follow up.

- **Initial assessment**

In general the following steps should be taken in the initial evaluation of MDR-TB patients who are female and in the reproductive age group.

- Initial pregnancy testing for all women of child-bearing age
- If pregnancy test is negative, contraceptives are strongly recommended during MDR-TB treatment
- Pregnant patients should be carefully assessed, taking into consideration;
    - ✓ Gestational age and

- ✓ Severity of the drug-resistant TB.

☛ **What is the best time to start treatment in patients with MDR- TB who are pregnant?**

The general principle is that the risks and benefits of treatment should be carefully considered and all options should be discussed with the mother. Majority of teratogenic effects occur when the drugs are taken in the first trimester. Ideally avoid treatment during first-trimester, however, if the disease is severe consider treatment regardless of trimester. Initiate MDR-TB therapy during second or third trimester to achieve smear conversion prior to delivery of the baby.

Give priority to the mother when her disease is severe and life threatening. Avoid treatment initiation during the first trimester when there is no such condition for the sake of avoiding potential fetal harm.

Decision to postpone the start of treatment is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks).

General principles regarding treatment of pregnant patients with MDR-TB:

When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used.

- Then reinforce with an injectable agent and possibly other drugs immediately postpartum.
- Pyridoxine should be given for all MDR cases with Pregnancy.
- If pregnancy occurs while on treatment, refer patient to the treatment initiating centre for subsequent treatment decision.

☛ **Are there drugs that need to be avoided during pregnancy?**

1. Aminoglycosides

Aminoglycosides are potentially toxic to the developing fetal ear and should not be used in the regimens of pregnant patients.

If an injectable agent cannot be avoided (in life threatening or severe disease) **Capreomycin**is the drug of choice, though it may carry the same risk of ototoxicity.

2.Ethionamideand **prothionamide**

If possible, Ethionamide should be avoided in pregnant patients because teratogenic effects have been observed in animal studies. Ethionamide can increase the risk of nausea and vomiting associated with pregnancy. The recommended regimen is **E-Z-(Cm)-Lfx-Cs-PAS**

Breast Feeding

Most TB drugs cross into the breast milk at low levels. Mothers receiving INH, cycloserine and ethionamide and their breastfed infants should be supplemented with vitamin B6 (pyridoxine). The doses of TB drugs that babies receive via breast milk are insufficient to treat or prevent TB in the infant. Small amounts of fluoroquinolones have been detected in human breast milk (WHO, 2014c). Because of the risk of arthropathy in immature animal models, the ATS does not recommend use of fluoroquinolones during breastfeeding. However, in the setting of

MDR-TB, where fluoroquinolones play such an essential role, the potential benefit may outweigh the potential risk. In these situations, the family should be informed of the theoretical risk.

In general a woman who is breastfeeding and has drug-resistant TB should receive a full course of MDR-TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her Baby. Sputum conversion should be achieved as soon as possible to prevent transmission of infection to the baby. Any effects on infants of such exposure during the full course of MDR-TB treatment have not been established.

There is no proven harm to the breast feeding child by second line anti TB drugs so far. So breast feeding mother with MDR-TB should be treated with full course of second line anti TB drugs with no exception. Proper infection prevention precautions should be observed to reduce risk of transmission of the bacilli to the child

Contraception

Birth control is strongly recommended for all non-pregnant sexually active women receiving therapy for drug-resistant TB because of the potential consequences for both the mother and fetus resulting from drug-resistant TB treatment during pregnancy (WHO, 2010). There is no contraindication to the use of oral contraceptives with non rifamycin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment medications. Patients, who vomit at any time directly after, or within the first two hours after taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets being tolerated.

MDR-TB treatment is not a contraindication to the use of oral contraceptives. In fact Contraception is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB because of frequent and severe ADRs to the mother, teratogenicity of treatment to the fetus and risk of transmission to the new born.

- Preferred options for contraception are:
  - ✓ Injectables/Implants (preferable for patients who have vomiting)
  - ✓ IUCDs
  - ✓ Barrier methods like Diaphragm/Condom
  - ✓ OCPs(if no Rifampicin)

All patients are encouraged to use condoms to protect against sexually transmitted disease including HIV. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-tuberculosis treatment.

Patients who vomit at any time directly after, or within the first two hours after, taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated. Other methods of contraception such as injectables and IUCDs should be used if patients continue to experience frequent vomiting.

Diabetes Mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. The presence of diabetes mellitus may potentiate the adverse effects of anti-tuberculosis drugs, like renal dysfunction and Peripheral neuropathy. Diabetic patients

are 3-5 times more likely to develop TB. TB (both sensitive and resistant) is more difficult to diagnose in patients with diabetes due to its atypical chest radiographic presentation and more frequent extra pulmonary disease (CARE II; 2012).

Management of diabetic patients with MDR-TB may be more difficult due to:

- Overlapping symptoms of toxicity of SLDs and complication of DM(e.g. neuropathy, renal failure)
- Existing diabetes complications may make administration of certain SLD difficult or impossible (e.g. Neuropathy, nephropathy)
- Increased pill burden due to use of oral hypoglycemic agents and drugs for complications of diabetes along with SLD.
- Possible drug -drug interactions.
- Glycemic control may become an issue; i.e. Ethionamide may make blood sugar control difficult.
- Patients with DM tend to be older than TB patients in general, further complicating their management

In General the following management principles should be applied.

- Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but patient may require frequent monitoring of blood sugar and dose adjustment.
- Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.
- DOT of diabetes medications may help improve outcome of tuberculosis

Renal Insufficiency

Compared to the general population, patients with chronic renal failure undergoing hemodialysis are at a 10- to 25-fold increased risk of developing tuberculosis (TB) once infected. These patients require careful monitoring for treatment of TB, and drug-resistant TB in particular (Peloqui*et al.*, 2004; Czock*et al.*, 2006). Data regarding clearance of anti-tuberculosis drugs are best documented for patients with creatinine clearance less than 30 ml/minute, or for those undergoing hemodialysis. For individuals with mild renal failure or undergoing peritoneal dialysis, the data are less available (Czock*et al.*, 2006). In addition to the effects on drug clearance, the diseases that cause renal failure and concomitant treatments can also impact drug levels (by altering absorption or drug interactions).

Patients with MDR-TB may have renal insufficiency at the time of MDR-TB diagnosis or they may develop it later while on treatment secondary to use of injectables. Base line BUN and creatinine should be done routinely for every patient to be started on SLDs. The lab tests should also be subsequently monitored monthly for those with normal baseline RFT and more frequently for those with abnormal test and with diabetes mellitus.

Patients with the following conditions have higher risk of developing renal insufficiency and hence require close follow-up:

- Diabetes Mellitus
- Hypertension
- History of prolonged usage of amino glycosides
- Elderly
- Prolonged duration of TB illness

Great care should be taken in managing MDR-TB patients with renal insufficiency. The dose and/or the interval between dosing should be adjusted based on the GFR. Consultation should be made with the treatment center when making dose adjustment and if there is any evidence of deterioration of renal function while on treatment such patients should be referred to the TIC for specialist care.

Liver Disorders and Toxicities

Many tuberculosis (TB) medications have the potential to cause hepatotoxicity, and their use must be contemplated in the setting of severe liver dysfunction. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of resistant disease do not affect the liver (Marra*et al.*, 2004).

The liver is one of the commonest organs which can be affected by anti TB drugs. Both first line and second line anti TB drugs can cause liver toxicity. On the other hand patients with MDR-TB who need second line anti TB drugs may have an underling liver disease. In both cases meticulous clinical and laboratory monitoring should be done to follow up the progress. Patients developing liver toxicity should be managed with supportive care and treatment modification as appropriate.

First-line drugs associated with hepatoxicity;

- Isoniazid
- Rifampicin it is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice.
- Pyrazinamide. it is the most hepatotoxic of the three drugs

Second-line drugs associated with hepatoxicity :hepatotoxicity is relatively less common with SLDs compared to any of the first line drugs

- Ethionamide,
- Prothionamide
- PAS
- Fluoroquinolones **(**Hepatitis occurs rarely)

Seizure Disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking antiseizure medication. If the seizures are not under control, initiation or adjustment of antiseizure medication will be needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected (Bartlett, 2011).In the treatment preparation evaluation of patient's history of current or past seizures should be included. If there is history of seizures further evaluation is needed.

- Is the patient on treatment for the seizure?
- When did the last attack of seizure occur?
- What was the underlying cause for the seizure (If it is known)
- If the cause is unknown, we may need to evaluate to know the cause.

Management considerations for patients with MDR-TB and seizure disorder

If the seizure is not under control, initiation or adjustment of anti-seizure medication will be needed before the start of drug-resistant TB therapy;

- In addition, any other underlying conditions or causes of seizures should be corrected.
- Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication.
- Cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anticonvulsant medication needs to be adjusted to control the seizure disorder.
- The risks and benefits of using cycloserine should be discussed with the patient and the decision to use cycloserine should be made together with the patient
- In mono- and poly-resistant cases, the use of Isoniazid and Rifampicin may interfere with many of the anti-seizure medications. Rifampicin causes fast metabolization of other drugs in the body. Thus, the serum level of the other drugs may decrease when taken together with Rifampicin.
- Seizures that present for the first time during anti-tuberculosis therapy are likely to be the result of an adverse effect of one of the anti-tuberculosis drugs. So revision of the regimen and titration of the anti convulsant medications is required.

Psychiatric disorders and MDR TB

It is advisable for psychiatric patients to be evaluated by a health care worker with psychiatric training before the start of treatment for drug-resistant TB. The initial evaluation documents and any existing psychiatric condition establish a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment (Vega *et al.,* 2004; Acha*et al.,* 2007). Any psychiatric illness identified at the start of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with drug-resistant TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for drug-resistant TB patients and may be helpful for patients with or without psychiatric conditions (Vega *et al.,* 2004; Acha*et al.,* 2007).

Evaluation for psychiatric disorders is very important at the initiation of MDR TB treatment and during follow up. Some of the reasons are:

- Baseline psychiatric disorders are very common among patients with MDR-TB due to the chronicity of the illness and the socioeconomic stressors associated with the disease.
- Psychiatric disorders can be important barriers to adherence
- Second line drugs like cycloserine commonly cause psychiatric disturbance like depression as a side effect.

Psychiatric evaluation during MDR-TB treatment

It is advisable for psychiatric patients to be evaluated by a health-care worker with Psychiatric training before the start of treatment for drug-resistant TB.

The initial evaluation should document:

- Any existing psychiatric condition and
- Establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment

Subsequently the patient should be evaluated for newly developing or worsening of existing psychiatric disorders and the problems should get a timely treatment.

Management options for psychiatric disorders in MDR-TB treatment

The management options are:

- Medical (drug) treatment.
- Individual counseling or group therapy. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions. Adequate measures to prevent infection risk should be in place for the group therapy:

The use of cycloserine is not absolutely contraindicated in the treatment of MDR-TB in psychiatric patients. Adverse effects from cycloserine may be more prevalent in psychiatric patients, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. So the following precautions should always be applied

- Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.
- All health-care workers treating drug-resistant TB Should work closely with a mental health specialist and have an organized referral system for psychiatric emergencies.

Health care workers should be watchful for signs of Psychiatric emergencies that include

- Psychosis,
- Suicidal ideation and
- Any situation involving the patient's being a danger to him or herself or others.

These manifestations are usually danger signs and such patients should immediately be referred to the Treatment Initiating Center after stabilization.

Substance dependence and abuse

Patients with substance dependence disorders should be offered treatment for their addiction, although active consumption is not a contraindication for anti-TB treatment. Complete abstinence from alcohol or other substances should be strongly encouraged but should not be pursued at the expense of compromising adherence to drug-resistant TB treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until measures to ensure adherence have been established. Patient-centred directly observed therapy gives the patient contact with and support from health care providers, which often allows complete treatment even in patients with substance dependence (Kang *et al.*, 2013).

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures; the drug is contraindicated in severe central nervous system disease . However, if central nervous system disease is not severe and cycloserine is considered important to the regimen, it can be used in these patients under close observation for adverse effects and prompt treatment if any develop (Kang *et al.*, 2013).

Substance abuse and dependence cause challanges in MDR-TB treatment such as:

- Poor adherence
- Higher occurrence of psychiatric disorders and other health problems.
- More frequent drug adverse effect of cycloserine.

Patients with substance dependence disorders should be offered treatment for their addiction whenever possible. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti-tuberculosis treatment.

However, if the treatment is repeatedly interrupted because of the patient's addiction, therapy should be suspended until successful addiction treatment or measures to ensure adherence have been established. Good DOT give the patient an opportunity to have frequent contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependency (Kang *et al.,* 2013).

1.2.1 Drug-resistant TB and HIV Co-management

HIV co-infection is a significant challenge for diagnosis, treatment and prevention of drug-resistant tuberculosis. Many reports have shown high mortality rates among HIV-infected patients with DR-TB, and alarming mortality rates in patients co-infected with XDR-TB and HIV (Walker *et al.,* 2009; Sergeev*et al.*, 2012). Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support, and strong infection control measures are all essential components in the management of DR-TB in HIV positive persons.

Diagnosis of DR-TB in HIV-positive Patients

The diagnosis of tuberculosis (including MDR-TB and XDR-TB) in HIV-positive people is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extra-pulmonary or sputum smear-negative than in HIV negative TB patients, especially as immune-suppression advances. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality (Walker *et al.,* 2009). Therefore HIV positive individuals suspected of having DR-TB should be urgently evaluated by DST preferably by the rapid molecular diagnostic tests for early diagnosis and treatment (CDC, 2008).

Monitoring of DR-TB and HIV therapy in co-infected patients

HIV treatment must be taken daily without exception to prevent the evolution of drug-resistance. DOT is particularly important in the setting of second-line antituberculosis therapy, since it can result in a large pill-burden and numerous side-effects that make taking ARVs more difficult.

The complexity of antiretroviral regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring.

Given that the regimens together are particularly difficult to take the following could be particularly challenging:

- The stigma associated with both diseases can result in serious discrimination,
- The risk of mortality is very high,
- Patients with HIV-associated DR-TB may require special socioeconomic, nutritional, and psychosocial support in order to successfully complete treatment.

1.2.2 MDR-TB in Children

Children may be less likely than adults to acquire resistance during the treatment of tuberculosis (TB) due to lower bacillary load. However, there is no reason to expect that children will evade infection by resistant strains of TB (Swaminathanand Rekha, 2010). When children have multi-drug resistant tuberculosis (MDR-TB), it is usually 'primary resistance', i.e., they are infected with strains transmitted from adults with MDR-TB. The rate of transmission of strains of MDR-TB has been shown to be the same for children as for adults and also the

incidence of primary drug resistance is similar among adults and paediatric cases (Swaminathanand Rekha, 2010; WHO, 2010).

How big is the problem of TB among children?

Surprisingly, there is little data to answer this question. According to the WHO, approximately 8.8 million people become sick with TB each year. However, most experts estimate 10 to 15 percent of these cases occur in children much higher than the number actually reported (Nelson and Wells, 2004; Marais and Schaaf, 2010).Because children are difficult to diagnose using the standard microscope method, which is the only test available in many high burden countries, the vast majority of childhood TB cases go unreported making it very difficult to determine the true burden of childhood TB that exists in the world (Marais *et al.,* 2010).

MDR TB Case Finding in Children

The diagnosis of active tuberculosis among children is difficult because of the lack of a standardized reliable case definition. Clinical presentation is variable and often subtle. Lower bacillary loads, which are common in pediatric tuberculosis, render microbiologic confirmation difficult (Ahmed andMokaddas, 2010). Up to 50% of children may remain smear- and culture-negative despite the presence of active disease. As a result, the identification of drug resistance, and thus the definitive diagnosis of MDR-TB, is particularly problematic among children (Zignol*et al.,* 2012). This is especially problematic for children with a clinical diagnosis of TB who are known to have a household contact with MDR-TB, or for children who live in 'hot spots' of MDR-TB transmission. Such children may have been infected with resistant strains of tuberculosis but, despite having active infection, remain smear and culture-negative.

It is essential to consider MDR-TB in children who are

1. Experiencing failure to first line treatment
2. Known to have household contact with a person known or suspected to have MDR-TB.

Treatment of MDR-TB in Children

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB should be guided by the DST results of the source case and the history of exposure to antituberculosis drugs of the source case. However, every effort should be made to diagnose MDR-TB in children as early as possible as delay in diagnosis is highly associated with increased mortality.

1.3 The Prevalence of MDR-TB and its magnitude

The epidemiology of MDR-TB is complicated by the fact that *Mycobacterium tuberculosis*, unlike many other infectious diseases, causes disease in only a minority of patients infected and has a lifetime potential for activation after infection. MDR-TB incidence varies considerably in different populations and geographical regions. Most of these differences can be attributed to underlying variation in the prevalence of infection; however, very often the underlying reasons for increased incidence are difficult to entangle. Descriptive epidemiology then becomes helpful in identifying populations and risk groups that need particular attention for targeting scarce resources (WHO, 2010).

The number of cases of MDR-TB, both new and old, present at a given time in a defined population. Prevalence is usually expressed as a proportion (%) or as a number per 100 000 population. Prevalence of MDR-TB can only be determined accurately through complicated and costly population surveys. Prevalence of MDR-TB in a

country or particular area is largely determined by the quality of chemotherapy and the TB treatment program which can be further fuelled by the conditions of the country such as extensive malnutrition, poverty, and HIV. In countries where there is not adequate treatment of MDR-TB, the prevalence of MDR-TB may be two to three times higher than the annual incidence (WHO, 2014a).

In 2008, an estimated 390 000–510 000 cases of MDR-TB emerged globally (best estimate, 440 000 cases).Among all incident TB cases globally, 3.6% are estimated to have MDR-TB. Almost 50% of MDR-TB cases globally are predictable to occur in China and India. In addition, in 2008, MDR-TB caused an estimated 150 000 deaths (WHO, 2010). According to WHO (2008), the increase in prevalence and incidence of MDR-TB are caused by concurrent factors such as inadequate treatment regimens, poor case holding, suboptimal drug quality and transmission of resistant strains (WHO 2008). Furthermore, one can speculate about the reasons that retreatment failure rates may be associated with higher rates of MDR- TB. The relationship may simply be an association without causation, i.e., that retreatment fails because a given patient may already have MDR- TB. In that sense, retreatment failure is simply a marker for preexisting MDR- TB. However, it is also possible that retreatment may be a cause of MDR- TB (WHO, 2014a).

The existing WHO recommendations for retreatment regimens could lead to development of MDR- TB or XDR-TB in many instances because suggested retreatment regimens potentially amount to addition of a drug to a failing regimen, thereby intensifying the level of drug resistance (Yanis*et al.,* 2008).Besides,WHO (2011) indicated that countries conduct surveillance of anti-TB drug resistance as component of any TB control programme with four main objectives: (i) measure the burden of drug-resistant TB and accurately plan treatment programmes with second-line drugs; (ii) assess epidemiological trends as a reflection of the effectiveness of implemented drug-resistant TB prevention and control activities; (iii) design effective empirical, standardized regimens for the treatment of TB, particularly for patients who have already been treated for TB and return with the disease; and (iv) promptly identify local outbreaks of drug-resistant TB in order to respond in a timely way (WHO 2011).Worldwide, the proportion of new cases with MDR-TB was 3.5% in 2013 and has not changed compared with recent years. However, much higher levels of resistance and poor treatment outcomes are of major concern in some parts of the world (WHO, 2014a).

Obviously, as reports revealed MDR-TB has emerged as a significant global health concern (Surendra*et al.,* 2011). To this view, there are upsetting reports of increasing drug resistance from various parts of the world which potentially threaten to disrupt the gains achieved in TB control over the last decade. As a result, drug resistance has reached alarming levels with the emergence of strains that are virtually untreatable with existing drugs.

Evidently, MDR-TB is essentially man-made phenomenon largely due to human error in any of management of drug supply, patient management, prescription of chemotherapy and poor patient adherence i.e. patients may feel better and halt their medication, mal-absorption (FMOH, 2011). In fact, it could be said that the occurrence of MDR-TB itself is an evidence of systematic failure of the community to tackle a curable diseases (Singh *et al.*, 2007). Previous treatment, age group between 25-44 year and less than 65 years, TB/HIV co-infection, poor living conditions, poverty and malnutrition, homelessness, alcohol abuse, prisons and overcrowding are the risk factors for MDR-TB (Kliiman, 2009). For instance in South Africa which is the world's third highest burden TB country, only lagging behind countries with significantly larger populations,

such as China and India, the numbers of MDR-TB patients have increased due to the concurrent HIV epidemic and inadequate management of TB (WHO, 2014a).

So far, the magnitude of the problem posed by MDR-TB has been estimated in about two thirds of all countries worldwide through disease surveillance and surveys (WHO, 2009). According to Alistair *et al.* (2010), each year new hot spots of MDR-TB are documented.Among others the countries that have been most MDR-TB prevalence reported are include Ethiopia, Indonesia, Nigeria, the Philippines, and Sudan, Cambodia, Zambia, Bangladesh, China, Democratic Republic of Congo, Egypt, India, Mexico, Russia, South Africa, and Ukraine (Alistair *et al.*, 2010). For instance, in Ethiopia, by 2008, WHO estimated the incidence MDR-TB among new TB cases to be 1.6 % (160 cases) and 11.8 % (5000 cases) among previously treated TB cases (WHO 2010). Additionally, MDR-TB was found in 32.3% and 75.6% of the new and previously treated patients, respectively, and 11.9 % of the 612 patients found to have MDR-TB had XDR-TB. Likewise, MDR-TB is very common among TB patients throughout Belarus (Alena *et al*., 2013).

Globally, in 2013, there were an estimated 480,000 new cases of MDR-TB, and WHO estimates that 9% of these cases were XDR-TB. MDR-TB has been reported in most countries, with 27 countries identified as having a high burden of MDR-TB specifically (WHO, 2014a). XDR-TB has been reported in 100 countries and territories (Table 3).

Table 3. TB cases by incidence, prevalence and mortality by region, 2013 (Source: adapted from The U.S. Government and Global Tuberculosis, 2015).

Region	Incidence			Prevalence		Mortality	
	Number (in thousands)	%	Rate (per 100,000 population)	Number (in thousands)	Rate (per 100,000 population)	Number (in thousands)	Rate (per 100,000 population)
Africa	2,600	29%	280	2,800	300	390	42.0
Americas	280	3%	29	370	38	14	1.5
E. Mediterranean	750	8%	121	1,000	165	140	23.0
Europe	360	4%	39	460	51	38	4.1
South-East Asia	3,400	38%	183	4,500	244	440	23.0
Western Pacific	1,600	18%	87	2,300	121	110	5.8
Global Total	**9,000**	**100%**	**126**	**11,000**	**159**	**1,100**	**16.0**

1.3.1 Epidemiology of MDR-TB

Globally, in 1994 to 2010 multidrug resistance was observed in 3.4% and 19.8% of all new TB cases and previously treated TB cases respectively. The 2011 WHO Global TB Report estimated the presence of 650 000 cases of MDR-TB among the world's 12.0 million prevalent cases of TB. However, diagnosis and appropriate treatment of multidrug-resistant TB (MDR-TB) remain major challenges. Less than 5% of new and previously treated TB patients were tested for MDR-TB in most countries in 2010. Similarly, there is a challenge to initiate treatment for confirmed MDR-TB cases. In 2010, only 46,000 MDR-TB cases were enrolled for the treatment which is equivalent to only 16% of the 290 000 cases of MDR-TB estimated to exist among notified TB patients in 2010.

The epidemiology of MDR-TBis the study of the spread of MDR-TB and the factors determining the spread of disease in human populations. Epidemiology is also the basic science for preventive medicine and public health. The epidemiologic framework for understanding the dynamics of MDR-TB in a community pertains to three types of epidemiologic questions:

• **Analytic epidemiology** (also called etiologic epidemiology), aimed at disentangling and identifying factors that increase the likelihood of infection and the development of disease;

• **Descriptive epidemiology,** that outlines the frequency and distribution of infection, disease and death from MDR-TB in different populations;

• **Predictive epidemiology,** using modelling techniques to forecast the likely course of a MDRTB epidemic in a given community, based on historical observations.

1.3.2 The Global Burden of MDR -TB

The emergence of MDR-TB has become a major global health concern to many countries, especially those in low and middle-income settings. Among all cases of TB globally, WHO estimates that nearly 4% of new cases and 20% of retreatment cases are multidrug-resistant (WHO, 2014a).

A global estimate of MDR-TB prevalence was included in the 2011 and 2012 global TB reports, with a best estimate of 630 000 cases in 2011 (WHO, 2014a).Updated global estimates of MDR-TB incidence and mortality (best estimates of 450 000 incident cases and 150 000 deaths in 2012) were presented in the 2013 global TB report. Recently, WHO estimates more than 2 million people will develop MDR-TB between 2011 and 2015 (WHO, 2014a). Furthermore, MDR-TB in 2012, which is 5% of the 31004 patients for whom there were drug susceptibility test results (CDC, 2014; Nishi *et al.*, 2014; WHO, 2014a). Although the Millennium Development Goal (MDG) to halt and reverse the TB epidemic by 2015 has been achieved, the global burden of TB remains enormous with 8.7 million new cases recorded in 2011 (WHO, 2012).

Ibrahim *et al.* (2013) noted that the frequency of MDR-TB varies greatly between countries. Furthermore, WHO estimates roughly 630 000 cases of MDR-TB worldwide, with great variation in the frequency of MDR-TB between countries (WHO, 2014b). Collected data confirm that Eastern European and central Asian countries continue to be the regions with the highest levels of MDR-TB, with MDR-TB accounting for nearly one third of

new TB cases and two thirds of previously treated TB cases in some settings (WHO, 2012). There were an estimated 450 000 new MDR-TB cases in 2012, about half of which were in India, China and the Russian Federation.

According to analyzed data by Dennis *et al*. (2013) which reported to WHO by 30 countries, expected to have more than 1000 MDR-TB cases among notified patients with pulmonary tuberculosis in 2011. Accordingly, in the 30 countries, 18% of the estimated MDR-TB cases were enrolled on treatment in 2011. Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraine each detected and enrolled on treatment more than 50% of their estimated cases of MDR-TB. In Ethiopia, India, Indonesia, the Philippines, and Russia, enrolments increased steadily between 2009 and 2011 with a mean yearly change greater than 50%: however, in these countries enrolment in 2011 was low, ranging from 4% to 43% of the estimated cases. In the remaining countries (Afghanistan, Angola, Azerbaijan, Bangladesh, China, Democratic Republic of the Congo, Kenya, Kyrgyzstan, Moldova, Mozambique, Burma, Nepal, Nigeria, North Korea, Pakistan, South Korea, Thailand, Uzbekistan, and Vietnam) progress in detection and enrolment was slower. In 23 countries, a median of 53% patients with MDR-TB successfully completed their treatment after starting it in 2008 to 2009.

Moreover, today, together with the burden of infection due to Human Immunodeficiency Virus (HIV), this co-infection drives most of the TB morbidity and mortality in many areas like Africa and makes more complicated its control and decrease in many terms (TB Alliance, 2012b). Besides, Diana and Alfonso (2013) recently showed that TB is a human danger and still a significant public health problem in the world, but particularly in developing nations. For instance, patients in India, China, the Russian Federation and South Africa account for nearly 60% of the world are MDR-TB (WHO, 2012).

The number of new casesof MDR-TB diagnosed during the course of one year. Incidence is expressed as a proportion of the mid-year population and as a standardized rate per 100 000 population. True incidence is almost impossible to determine, as incidence is directly related to case finding and notification; as a result of limitations of case finding and notification systems, incidence is frequently referred to as ‘notified incidence’ or ‘estimated incidence’, derived from epidemiological models using mortality, prevalence, and risk of infection.

The number of MDR-TB deaths occurring in a population during one year, usually expressed as a rate per 100 000 population. The proportion of MDR-TB patients who die as a result of the disease within a given period, usually reported on an annual time period (Diana and Alfonso, 2013).

2. Convergence of the epidemics of MDR-TB and HIV infection

At no time in recent history has TB become of great concern as today. Despite highly effective drugs, disease and deaths due to *Mycobacterium tuberculosis* are increasing globally fuelled by the HIV epidemic (WHO, 2014a). Study revealed that the human immunodeficiency virus (HIV) is a driving force behind the global burden of TB and the development of drug-resistant TB (Isaakidis*et al*., 2012). Besides, HIV infection has been globally recognized as an important risk factor for increased susceptibility to TB infection and the risk of

developing active TB (Isaakidis*et al*., 2013). Similarly, TB is one of the major causes of death amongst people with HIV globally (Isaakidis*et al*., 2012; WHO, 2013). Furthermore, HIV positive cases are also more likely to have extra-pulmonary disease than non-HIV infected cases. HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of MDR and XDR-TB (Neel *et al.*, 2010). HIV is a powerful risk factor for development of all forms of TB including DR-TB and for this reason, DR-TB is often associated with higher mortality rates in HIV infected when compared with the non-infected (Mrinalini*et al*., 2014).

The synergy between TB and HIV is strong i.e., in high HIV prevalence population, TB is a leading cause of morbidity and mortality, and HIV is driving the TB epidemic in many countries, especially in sub-Saharan Africa (CDC, 2013).Consequently, the spread of TB and HIV is aggravated by socio-economic factors such as poverty and low levels of literacy (WHO, 2007). Moreover, MDR-TB patient co-infected with HIV is subject to long and potentially toxic treatment that may make the patient debilitated stressed, and de-motivated (Isaakidis*et al*., 2012). Additionally, dependence on the family for support, discrimination, and/or financial problems can further influence the mental wellbeing of patients (Mrinalini*et al*., 2014). Consequently, management of MDR-TB patients co-infected with HIV is highly challenging. With growing evidence showing psychiatric illnesses such as depression, anxiety and psychosis to be associated with MDR-TB and HIV mental health care for patients with these two stigmatizing and debilitating diseases demands attention (Vega *et al.*, 2004;Ownby*et al.*, 2010; Isaakidis*et al*., 2012; Mrinalini*et al*., 2014).

According to WHO (2013), recent global data have shown rising rates of drug-resistant TB in sub-Saharan Africa, the region also suffering from the world's highest burden of HIV/AIDS. Kiliman (2009) noted that, the percentage of MDR-TB among HIV infected individuals was found to be three times higher. Among 136 suspected cases of MDR-TB, HIV-infection was confirmed among 114 (88%) in South Africa (Scott *et al.*, 2010). Likewise, Federal Ministry of Health of Ethiopia (FMOH, 2007) has documented that the human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of TB at all levels.

Generally, as implication of HIV infection and MDR-TB convergence, given the severe consequences of HIV infection and MDR-TBoccurring together, as well as the geographic overlap in manysettings, major consequences for HIV treatment and care and for addressing MDR-TB control can be anticipated (Wells *et al.*, 2007).

2.1 Global burden of tuberculosis and HIV Co-infection

TB and HIV act in deadly synergy (WHO, 2007). HIV infection increases the risk of TB infection on exposure, progression from latent infection to active TB, risk of death if not timely treated for both TB and HIV and risk of recurrence even if successfully treated. Correspondingly, TB is the most common opportunistic infection and cause of mortality among people living with HIV, difficult to diagnose and treat owing to challenges related to co-morbidity, pill burden, co-toxicity and drug interactions (Isaakidis*et al.*, 2011; WHO, 2012).

Worldwide about 11.1 million adults are co-infected with TB and HIV (FMOH, 2007). For instance, 70% of co-infected people are living in sub-Saharan Africa 20% in South East Asia and 4% in Latin America and the Caribbean, respectively. On the other hand, approximately half a million people worldwide were diagnosed with MDR-TB in 2006; more than 50 countries by the end of last year, including the United States, had reported XDR-TB (WHO, 2007; CDC, 2013). Likewise, in Ethiopia routine data from 44 sites in the year 2005/6 showed 41% of TB patients are HIV positive. Another routine data collected in 2006/7 showed that the co-infection is

31% (FMOH, 2011). Recently, WHO (2014a) documented that in 2013, 1.5 million people died from TB, including 360 000 among people who were HIV-positive with 1.1 million cases among people living with HIV.

2.2 Risk factors for MDR-TB

According to Espinal*et al.* (2001) and Caminero (2005), the global increase in drug resistance, particularly MDR-TB, reflects, at least in part, inappropriate use of anti-TB drugs during the treatment course of TB patients with drug susceptible strains. Additionally, investigations have broadly described that the risk factors of TB may be biomedical (such as HIV infection, diabetes, tobacco, malnutrition, silicosis, malignancy), environmental (indoor air pollution, ventilation) or socioeconomic (crowding, urbanization, migration, poverty) factors have been shown to be associated with the increased prevalence of MDR-TB (Faustini *et al*., 2006; Gulam, 2012).

2.2.1 Effect of treatment and Failure of retreatment in chronic TB patients

Previous treatment has been widely recognized as inducing multidrug resistance of *Mycobacterium tuberculosis* and the prevalence of MDR-TB has been estimated to be up to 10 times higher after unsuccessful treatment (Pablo-Me ńdez*et al.,* 1998). On the other hand, Chronic TB patients are defined as patients who are sputum positive at the end of the intensive phase and on completion of re-treatment regimen. These patients have the highest MDR-TB rates, often greater than 80% (WHO, 2008). Furthermore, for the relapse and default, erratic drug intake or early relapse may point to possible MDR-TB. Relapses within the first six months post treatment may have similar MDR-TB rates as failures. Repeated interruption of treatment can also result in selection for resistant mutants. Exposure to a confirmed MDR-TB patient is also another important issue (CDC, 2012). Accordingly, most studies have shown that close contacts of MDR-TB patients have very high rates of MDR-TB. This includes children, who should be started on MDR-TB therapy empirically until proven not to have MDR-TB (WHO, 2008).

2.2.2 Influence of immigration

Immigration has been suggested as one factor leading to the increased prevalence of MDR-TB in European countries (Espinal*et al.,* 2001; CDC, 2012). The association between MDR-TB and being foreign born could be due to a higher risk of transmission of MDR strains of *Mycobacterium tuberculosis* for immigrants, but it may be confounded by previous treatment. To this view, a French study stratifying results by country of birth found a higher risk of MDR-TB in both new and previously treated patients from sub-Saharan Africa, while patients from North Africa were at higher risk of MDR-TB only after a previous treatment (Schwoebel*et al.,* 1998).

2.2.3 Role of HIV

Numerous MDR-TB outbreaks have been documented in HIV positive individuals as a result of the depressed immune system and high susceptibility to infection (WHO, 2008). Initially it seemed that HIV status was a risk factor for MDR-TB, but nosocomial outbreaks largely accounted for the association and, currently, the prevalent hypothesis is that HIV infection favours the transmission of multidrug resistant strains of *M. tuberculosis* (McCray and Onorato, 2000). WHO documented that medical risk factors include co-infection with HIV; people with HIV are 21 to 34 times more likely to develop TB, and accounted for about 13% of all TB cases globally in 2010. Development of the disease is also linked to certain social risk factors, notably drug or alcohol abuse, poor housing conditions, homelessness and imprisonment (WHO, 2010).

2.2.4 Previous history of tuberculosis treatment

Several studies reported that previous history of anti-tuberculosis treatment is the most widely reported risk factor for MDR-TB. Previously treated TB has strongest association with MDR-TB in addition to the duration of previous TB treatment Patients who received previous anti-tuberculosis treatment had a 4-fold increased odds of multidrug resistance(Kiliman, 2009; Kai and Altraja, 2009; Alistair *et al.,* 2010).

2.2.5 Age and MDR-TB

Reports indicated that younger age is known to be the significant contributor for development of MDR-TB (Fairlie, 2011; ECDC; 2012). Contrary to this, the study conducted in South Africa showed that age was not a significant risk factor, it was found that MDR-TB was cultured from the blood in patients as young as 8 years and as old as 62 years (Scott *et al.,* 2010). Moreover, as WHO (2010) report indicated in a surveillance data collected from 13 countries of Central and Eastern Europe, the frequency of MDR-TB was much higher in all age groups compared with the rest of the countries (all high-income) and peaked in young adulthood (WHO 2010). On the other hand, WHO report noted that TB affects more men than women, and mostly adults in their productive years (WHO, 2012). However, all age groups are at risk but more than 95% of cases occur in developing countries. Furthermore, there was a clear association observed between MDR-TB and age under 65 years, but the association was weak and more heterogeneous for ages under (Espinal*et al.,* 2001; Fairlie, 2011). This can reflect the year in which effective anti-tuberculosis drugs such as rifampicin were introduced (Pablo-Me ńdez*et al.,* 1998).

2.2.6 Sex and MDR-TB

According to WHO (2010) drug resistance surveillance report, among 38 countries and 3 territories the odds ratio of harbouring MDR-TB strains for female TB cases compared with male TB cases was 1.1, showing no overall association between MDR-TB and sex of the patient. In South Africa, although a higher number of male than female MDR-TB cases were reported (4826 and 4615 cases, respectively), data from a total of 81,794 TB patients with known sex (95% of all patients) indicates that female TB cases have a 1.2 times higher odds of harbouring MDR-TB strains than male TB cases. Data from Australia, the Netherlands and the United States of America also show a higher risk of MDR-TB in female patients (WHO 2010). On the other hand, MDR-TB patients were more likely to be male in Western Europe, where previous treatment was the most important determinant of MDR-TB. In Eastern Europe, where the risk of transmission is greater, male sex was not a risk factor for MDR-TB. Hence, it could be hypothesized that women are more compliant with treatment and therefore less likely to receive inadequate treatment (CDC, 2012).

In a study conducted in Peru among 673 patients, more than half of diagnosed and confirmed (60.8%) MDR-TB was male which shows that gender is a risk factor for the development of MDR-TB (Molly *et al.,* 2008). Furthermore, in a systematic review conducted by Faustini *et al.* (2006), there was a stronger association of being a male sex as a risk factor for MDR-TB in the eight studies carried out in Western Europe and heterogeneity between studies were very low. Men were at lower risk of MDR-TB in the three studies carried out in the former USSR with a high heterogeneity between studies. Moreover, People living with HIV have a higher risk of MDR-TB (Wells *et al.,* 2007; Dubrovina*et al*., 2008; WHO, 2008). Generally, people living with HIV are particularly vulnerable to the impact of drug resistant TB due to the difficulties and delays in the diagnosis (Wells *et al.,* 2007), complications of concomitant treatment with TB and antiretroviral therapy (ART) (Havlir*et*

al., 2008) and poor TB infection control measures in many HIV care settings (Gandhi *et al.*, 2006; Kawai *et al*., 2006; ECDC, 2013).

2.2.7 Poor TB Treatment Adherence

Adherence to treatment means that a patient is following the recommended course of treatment by taking all the prescribed medications for the entire length of time necessary. On the other hand, adherence can influence the emergence of new disease strains, individual health outcomes, and the overall cost of health care (Comstock, 1999). For example, MDR-TB emerged largely because of widespread no adherence to treatment for TB disease. Poor adherence to treatment remains a major obstacle to efficient TB control in developing countries. Innovative strategies to improve access and adherence to treatment are needed. Poor adherence were related to age differences as younger patients are often occupied by study, work or other activities on a daily basis, in contrast with the more sedentary lifestyle post-retirement age (Law *et al.* 2008).

2.2.8 Site of TB Involvement

The clinical manifestations of TB are of two types: Pulmonary and Extra-pulmonary forms of TB (EPTB), the former being the commonest (Robert, 2013). Pulmonary TB features (Cough, fever, sweats, weight loss and haemoptysis) and extra-pulmonary lymphnode swelling (lymphadenitis) are leads that used in identifying diseases symptomatically (Gizachew*et al.,* 2013). In EPTB highly vascular areas such as lymph nodes, meninges, kidney, spine and growing ends of the bones are commonly affected. The other sites are pleura, pericardium, peritoneum, liver, gastro-intestinal tract, genito-urinary tract and skin. Before the advent of the HIV epidemic, approximately 85% of reported tuberculosis cases were pulmonary only, with the remaining 15% being extra-pulmonary or both pulmonary and extra-pulmonary sites (Farer *et al*., 1979).

In a study conducted elsewhere by Law *et al*. (2008) noted that, the vast majority of MDR-TB cases suffered from pulmonary TB (98%), and only 2% presented with extra pulmonary TB alone. On the contrary, a study conducted in South Africa indicated that about one quarter of drug resistant TB patients were diagnosed with extra-pulmonary TB in addition to pulmonary TB (Andrews *et al*., 2010). Another study conducted in Tomsk, Russian Federation, revealed that sputum-smear positivity was significantly associated with MDR-TB (Gelmanova*et al.*, 2007).

3. Causes of drug-resistant tuberculosis

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli (Joshi and Jajoo, 2010). Besides, an inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB (Joshi and Jajoo, 2010). However it should be stressed that MDR-TB is a man-made phenomenon such as poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.

Resistance to isoniazid and rifampicin drugs was reported in earlier reports (Zhang *et al.*, 1992; Telenti*et al.*, 1993; Piatek*et al.*, 2000). Accordingly, resistance to isoniazid is due to mutations at one of two main sites, in either the *katG* or *inhA* genes while resistance to rifampicin is nearly always due to point mutations in the *rpo*gene in the beta subunit of DNA-dependent RNA polymerase. These mutations are not directly connected, and so separate mutations are required for organisms to change from a drug-susceptible isolate to MDR-TB.

In addition, CDC (2012) report indicated that resistance to anti-TB drugs can occur when isoniazid and rifampicin drugs are misused or mismanaged. Examples include when patients do not complete their full course of treatment; when healthcare providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality (CDC, 2012). Biologically however, drug resistance develops in bacteria because of naturally-occurring changes in their genes. When bacteria are treated with a drug, these changes allow some to survive. Continued exposure to the drug kills any remaining drug-susceptible bacteria, providing the ideal environment for the resistant forms to flourish. Eventually that strain of bacteria can become completely resistant to the drug in question. Bacteria may develop resistance to more than one drug (WHO, 2012).

4. Prevention of MDR-TB

The emergence of resistance to drugs used to treat TB, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective TB control (Central TB Division, 2006; SairaZai*et al.*, 2010). Investigation noted that poor treatment practices breed drug resistance. Areas with a poor TB control tend to have higher rates of drug resistant TB. On the other hand, it has been acknowledged that good treatment is a pre-requisite to the prevention of emergence of resistance (Keshavjee and Farmer, 2010). Furthermore, the most important thing a person can do to prevent the spread of MDR- TB is to take all of their medications exactly as prescribed by their health care provider (WHO, 2013). No doses should be missed and treatment should not be stopped early (Jain and Dixit, 2008). Patients should tell their health care provider if they are having trouble taking the medications. If patients plan to travel, they should talk to their health care providers and make sure they have enough medicine to last while away (ECDC, 2014; WHO, 2014a). Additionally, all patients with DR-TB must be offered HIV counseling and testing, and those who are co- infected must be started on cotrimoxazole and antiretroviral treatment (ART) as soon as ARVadherence counseling is completed. All co-infected MDR/XDR-TB/HIV patients qualify to receive antiretroviral therapy (ART) regardless of their CD4 count (WHO, 2013). Earlier reports by Paramsivan (2003) and Davies (2003)noted that the key to the successful prevention of the emergence of drug resistance is adequate case finding, prompt and correct diagnosis, and effective treatment of infected patients. This can be achieved through the use of Directly Observed Therapy Short-course (DOTS).

Generally, prevention of emergence of MDR-TB in the community is more imperative rather than its treatment. It is impossible to tackle the problem of drug-resistant TB through treatment alone; each MDR-TB case costs more than 20 times the cost of a simple drug-susceptible TB case. Therefore basic TB diagnostic and treatment serviceswould be prioritized with the view that DOTS reduces the emergence of MDR-TB, andtherefore the need for Programmatic Management of Drug-Resistant TB (PMDT) over time (Udwadia, 2001; SairaZai*et al.*, 2010).

Conclusion

In this article, it is noted that Tuberculosis (TB) remains a major global health problem. Globally, TB is the second largest cause of death from aninfectious agent after HIV/AIDS and in developing countries in particular. Antibiotic resistance is a growing impediment to the control of infectious diseases worldwide, TB being among them. Multidrug-resistant tuberculosis (MDR-TB) caused by *Mycobacterium tuberculosis* resistant to both

isoniazid (INH) and rifampicin (RMP) with or without resistance to other drugs is among the most worrisome elements of the pandemic of antibiotic resistance. Several reports indicated that previous exposure of anti-TB treatment increased the risk of MDR-TB worldwide besides other risk factors. Moreover, the convergence of MDR-TB and HIV has created a new and dangerous major epidemic and the epidemic of MDR-TB and HIV co-infection has been a wake-up call to the public health community globally. Therefore, strengthening rapid diagnostic assays to detect highly drug-resistant TB are essential in preventing delays in treatment of MDR-TB and limiting its spread. Moreover, development of new drugs to effectively treat both MDR-TB and XDR-TB in shorter period of time is urgently needed.

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